

1           **PACKAGING AND DELIVERY OF PHARMACEUTICALS AND DRUGS**

2           The present application claims priority from U.S. Provisional Application Serial  
3   No. 60/214,578, filed June 28, 2000.

4                           **FIELD OF THE INVENTION**

5           The present invention relates generally to the field of metering, packaging and  
6   delivery of pharmaceuticals and drugs. Particular utility for the present invention is  
7   found in the area of facilitating metering and packaging of medications and drugs for  
8   inhalation therapy and will be described in connection with such utilities, although  
9   other utilities are contemplated, including liquid medication applications.

10                           **DISCUSSION OF THE PRIOR ART**

11           Certain diseases of the respiratory tract are known to respond to treatment by the  
12   direct application of therapeutic agents. As these agents are most readily available in  
13   dry powdered form, their application is most conveniently accomplished by inhaling  
14   the powdered material through the nose or mouth. This powdered form results in the  
15   better utilization of the medication in that the drug is deposited exactly at the site  
16   desired and where its action may be required; hence, very minute doses of the drug are  
17   often equally as efficacious as larger doses administered by other means, with a  
18   consequent marked reduction in the incidence of undesired side effects and medication  
19   cost. Alternatively, the drug in this form may be used for treatment of diseases other  
20   than those of the respiratory system. When the drug is deposited on the very large  
21   surface areas of the lungs, it may be very rapidly absorbed into the blood stream; hence,

1 this method of application may take the place of administration by injection, tablet, or  
2 other conventional means.

3 It is the opinion of the pharmaceutical industry that the bioavailability of the  
4 drug is optimum when the drug particles delivered to the respiratory tract are between  
5 1 to 5 microns in size. When the drug particles need to be in this size range the dry  
6 powder delivery system needs to address a number of issues:

7 (1) Small size particles develop an electrostatic charge on themselves during  
8 manufacturing and storage. This causes the particles to agglomerate or aggregate,  
9 resulting in clusters of particles which have an effective size greater than 5 microns.  
10 The probability of these large clusters making it to the deep lungs then decreases. This  
11 in turn results in a lower percentage of the packaged drug being available to the patient  
12 for absorption.

13 (2) The amount of active drug that needs to be delivered to the patient may be of  
14 the order of 10s of micrograms. For example, albuterol, in the case of a drug used in  
15 asthma, this is usually 25 to 50 micrograms. Current manufacturing equipment can  
16 effectively deliver aliquots of drugs in milligram dose range with acceptable accuracy.  
17 So the standard practice is to mix the active drug with a filler or bulking agent such as  
18 lactose. This additive also makes the drug "easy to flow". This filler is also called a  
19 carrier since the drug particles also stick to these particles through electrostatic or  
20 chemical bonds. These carrier particles are very much larger than the drug particles in

1 size. The ability of the dry powder inhaler to separate drug from the carrier is an  
2 important performance parameter in the effectiveness of the design.

3 (3) Active drug particles with sizes greater than 5 microns will be deposited  
4 either in the mouth or throat. This introduces another level of uncertainty since the  
5 bioavailability and absorption of the drug in these locations is different from the lungs.  
6 Dry powder inhalers need to minimize the drug deposited in these locations to reduce  
7 the uncertainty associated with the bioavailability of the drug.

8 Prior art dry powder inhalers (DPIs) usually have a means for introducing the  
9 drug (active drug plus carrier) into a high velocity air stream. The high velocity air-  
10 stream is used as the primary mechanism for breaking up the cluster of micronized  
11 particles or separating the drug particles from the carrier. Several inhalation devices  
12 useful for dispensing this powder form of medication are known in the prior art. For  
13 example, in U.S. Patent Nos. 3,507,277; 3,518,992; 3,635,219; 3,795,244; and 3,807,400,  
14 inhalation devices are disclosed having means for piercing or removing the top of a  
15 capsule containing a powdered medication, which upon inhalation is drawn out of the  
16 pierced or topped capsule and into the user's mouth. Several of these patents disclose  
17 propeller means, which upon inhalation aid in dispensing the powder out of the  
18 capsule, so that it is not necessary to rely solely on the inhaled air to suction powder  
19 from the capsule. For example, in U.S. Patent No. 2,517,482, a device is disclosed  
20 having a powder containing capsule placed in a lower chamber before inhalation,  
21 where it is pierced by manual depression of a piercing pin by the user. After piercing,

1 inhalation is begun and the capsule is drawn into an upper chamber of the device  
2 where it moves about in all directions to cause a dispensing of powder through the  
3 pierced hole and into the inhaled air stream. U.S. Patent No. 3,831,606 discloses an  
4 inhalation device having multiple piercing pins, propeller means, and a self-contained  
5 power source for operating the propeller means via external manual manipulation, so  
6 that upon inhalation the propeller means aids in dispensing the powder into the stream  
7 of inhaled air. See also U.S. Patent No. 5,458,135.

8         These prior art devices present several problems and possess several  
9 disadvantages which are remedied by the inhalation devices of the present invention.  
10 For instance, these prior art devices require that the user exert considerable effort in  
11 inhalation to effect dispensing or withdrawal of powder from a pierced capsule into the  
12 inhaled air stream. With these prior art devices, suction of powder through the pierced  
13 holes in the capsule caused by inhalation generally does not withdraw all or even most  
14 of the powder out of the capsule, thus causing a waste of the medication. Also, such  
15 prior art devices may result in uncontrolled amounts or clumps of powdered material  
16 being inhaled into the user's mouth, rather than a constant inhalation of controlled  
17 amounts of finely dispersed powder.

18         The above description of the prior art is taken largely from U.S. Pat. No.  
19 3,948,264 to Wilke et al, who disclose a device for facilitating inhalation of a powdered  
20 medication that includes a body portion having primary and secondary air inlet  
21 channels and an outlet channel. The secondary inlet channel provides an enclosure for

1 a capsule containing the powdered medication and the outlet channel is formed as a  
2 mouthpiece protruding from the body. A capsule piercing structure is provided, which  
3 upon activation forms one or more holes in the capsule so that upon vibration of the  
4 capsule by an electro-mechanical vibrator, the powdered drug may be released from the  
5 capsule. The piercing means disclosed in Wilke et al includes three radially mounted,  
6 spring-biased piercing needles mounted in a trochoidal chamber. Upon hand rotation  
7 of the chamber, simultaneous inward radial motion of the needles pierces the capsule.  
8 Further rotation of the chamber allows the needles to be retracted by their spring  
9 mountings to their original positions to withdraw the needles from the capsule. The  
10 electromechanical vibrator includes, at its innermost end, a vibrating plunger rod which  
11 projects into the intersection of the inlet channel and the outlet channel. Connected to  
12 the plunger rod is a mechanical solenoid buzzer for energizing the rod to vibrate. The  
13 buzzer is powered by a high energy electric cell and is activated by an external button  
14 switch. According to Wilke et al, upon inhalation through outlet channel 3 and  
15 concurrent pressing of switch 10d to activate the electromechanical vibrating means 10,  
16 air is sucked through inlet channels 4 and 12 and the air stream through the secondary  
17 inlet channel 4 raises the capsule up against the vibrating plunger rod 10a. The capsule  
18 is thus vibrated rapidly with powder being fluidized and dispensed from the pierced  
19 holes therein. (This technique is commonly used in manufacturing for dispensing  
20 powder through a hopper where the hopper is vibrated to fluidize the powder and  
21 move it through the hopper outlet. The pierced holes in the capsule represent the

1 hopper outlet.) The air stream through inlet channel 4 and 12 aids in withdrawal of  
2 powder from the capsule and carries this powder through the outlet channel 3 to the  
3 mouth of the user. (Wilke et al, column 3, lines 45-55). Wilke et al further discloses that  
4 the electromechanical vibrator means may be placed at a right angle to the inlet  
5 chamber and that the amplitude and frequency of vibration may be altered to regulate  
6 dispensing characteristics of the inhaler.

7 Thus, as noted above, the vibrator in Wilke et al's disclosed inhaler is an  
8 electromechanical device consisting of a rod driven by a solenoid buzzer. (This  
9 electromechanical means may be a motor driving a cam [Col. 4, Line 40]). A  
10 disadvantage of the inhaler implementation as disclosed by Wilke is the relatively large  
11 mechanical movement required of the rod to effectively vibrate the capsule. The large  
12 movement of the rod, usually around 100s of microns, is necessary due to the elasticity  
13 of the capsule walls and inertia of the drug and capsule.

14 Moreover, solenoid buzzers typically have operating frequencies less than 5 Khz.  
15 This operating frequency tends to be noisy and therefore is not desirable when  
16 incorporated into a dry powder inhaler from a patient's perspective. A further  
17 disadvantage of the electrochemical actuators of Wilke is the requirement for a high  
18 energy source (Wilke et al, Col. 3, line 38), thus requiring a large battery source or  
19 frequent changes of the battery pack for portable units. Both these features are not  
20 desirable from a patient safety and "ease of use" standpoint.

1           The inhaler of Wilke et al is primarily intended to reduce the amount of powder  
2 left behind in the capsule relative to other inhalers cited in the patent disclosure. (Wilke  
3 et al, Col. 4, lines 59-68, Col. 5, lines 1-48). However, Wilke et al does not address the  
4 need to deaggregate the powder into particle sizes or groups less than 5 microns in size  
5 as is required for effective delivery of the medication to the lungs; rather Wilke et al,  
6 like the prior art inhalers continues to rely on the air stream velocity to deaggregate the  
7 powder ejected into the air stream, into particle sizes suitable for delivery to the lungs.

8           Another prior art inhalation device is disclosed in Burns et al U.S. Patent No.  
9 5,284,133. In this device, a liquid medication is atomized by an ultrasonic device such  
10 as a piezo element (Burns et al, Col. 10, lines 36-51). A stream of air, usually at a high  
11 velocity, or a propellant then carries the atomized particles to the patient. The energy  
12 required to atomize the liquid medication in the nebulizer is prohibitively high, making  
13 this approach for the delivery of drugs to the lungs only feasible as a desk top unit. The  
14 high voltage requirements to drive the piezo, to produce the necessary mechanical  
15 displacements, also severely affects the weight and size of the device. It is also not  
16 obvious that the nebulizer operating principles can be applied to the dry powder  
17 inhalers for delivery of powder medication to the lungs.

18           The prior art devices therefore have a number of disadvantages which makes  
19 them less than desirable for the delivery of dry powder to the lungs. Some of these  
20 disadvantages are:

- 1           • The performance of the prior art inhalers depends on the flow rate generated  
2           by the user. Lower flow rate does not result in the powder being totally  
3           deaggregated and hence adversely affects the dose delivered to the patient.
- 4           • Inconsistency in the bioavailability of the drugs from dose-to-dose because of  
5           lack of consistency in the deaggregation process.
- 6           • Large energy requirements for driving the electromechanical based inhalers  
7           which increases the size of the devices making them unsuitable for portable  
8           use.
- 9           • Loss of medication from opened or topped capsules.
- 10          • Deterioration of medication in open or topped capsules due to exposure to  
11          oxygen or moisture.

12           In my prior U.S. Patent Nos. 6,026,809 and 6,142,146 (with Abrams), we provide  
13          an inhaler that utilizes vibration to facilitate suspension of a medication or drug into a  
14          gas that overcomes the aforesaid and other disadvantages and drawbacks of the above  
15          prior art. More particularly, the inhaler of our aforesaid patent includes a piezoelectric  
16          vibrator for vibrating the medication or drug. In a preferred embodiment of our  
17          aforesaid '809 and '146 patents, the medication or drug is supplied from a coiled tape  
18          having a plurality of spaced blisters or wells for carrying controlled aliquots of a dry  
19          powder medication or drug.



1 Referring to Fig. 1 which corresponds to Fig. 9 of our aforesaid '809 U.S. Patent,  
2 the medication or drug is packaged in a disposable drug cartridge 210 which includes a  
3 coiled tape 218 carrying a plurality of spaced flat walled blisters or wells 220 for  
4 containing controlled aliquots medication. A release film 221 covers and seals blisters  
5 or wells 220. Tape 218 is formed as a coil, and threaded between a first guide platen 222  
6 and pinch roller 224. Pinch roller 224 in turn is driven by a take-up spool 226 which in  
7 turn is driven by a thumbwheel 228 which is mounted on a common shaft with the  
8 take-up spool 226. In use, release film 221 is peeled from the tape 218, whereby to open  
9 blisters or wells 220, one at a time, as the film is advanced through the cartridge, and  
10 the release film 221 is collected on take-up spool 226.

11 Completing cartridge 210 is a piezoelectric element 232 for mechanically  
12 engaging the bottom wall of the opened blisters or wells 220, one at a time, as they are  
13 selectively advanced in position over and in contact with the piezoelectric element 232.  
14 Tape 218 also preferably includes detent means or the like for indexing the tape so that  
15 a selected opened blister or well 220 is automatically positioned over piezoelectric  
16 element 232. Finally, an actuating circuit and power supply (not shown) is mounted  
17 within cartridge 210.

18 Preferably, but not necessarily, the interior walls of the housing are coated with a  
19 metallized coating 234 so as to obviate possible electrostatic charge buildup within the  
20 housing.

1           Also, if desired, an auxiliary air inlet 236 may be provided immediately upstream  
2 of the piezoelectric element 232 for assisting in carrying particles as they are energized  
3 by the piezoelectric element.

#### 4                                   BRIEF DESCRIPTION OF THE INVENTION

5           The present invention provides an improvement over the medication packaging  
6 and delivering technology described in our aforesaid '809 and '146 patents. More  
7 particularly, in accordance with the present invention, controlled aliquots or doses of a  
8 medication or drug are pre-packaged in a blister pack. The blister pack includes a  
9 frangible crowned top element which may be conical, conical with a rounded point,  
10 rounded, or other raised shape configuration, and a bottom element which may be a flat  
11 web or membrane, or which itself may be of shaped configuration, e.g. conical, round,  
12 dish shaped, etc. for closely engaging with an underlying piezo element. The shape  
13 and size of the blisters is chosen to provide optimum controlled delivery of controlled  
14 amounts of controlled size particles of a given medication or drug. Before being  
15 delivered, the top element of the blister pack is pierced with a piercing device such as a  
16 sharp needle to form one or more apertures for delivery of the medication or drug  
17 contained within the blister pack. The hole pattern and hole size is selected to provide  
18 optimization of delivery of the particular medication or drug packaged therein. The  
19 holes also may act as filters whereby to prevent ejection from the blisters of aggregated  
20 or agglomerated particles, until the particles are broken up to optimal size by energy  
21 input from the piezo. Thus, in the case, e.g. of a dry powder medication or drug or a

1 liquid medication or drug, particle size and dose of the medication or drug delivered  
2 can be optimized, and tailored to the frequency of the piezo. Typically, the bottom  
3 blister element is placed on/in close proximity to the piezo prior to or  
4 contemporaneously with piercing the top element. The top element is pierced, and  
5 activation of the piezo drives the medication or drug from the blister pack through the  
6 perforations in the top element.

#### 7 BRIEF DESCRIPTION OF THE DRAWINGS

8 Other features and advantages of the present invention will be seen from the  
9 following detailed description, taken in conjunction with the accompanying drawings,  
10 wherein:

11 Figs. 1a and 1b are schematic representations of a dry powder packaging and  
12 delivery system in accordance with the prior art;

13 Figs. 2 - 5 illustrate various blister packs made in accordance with the present  
14 invention; and

15 Figs. 6A and 6B illustrate a plurality of blister packs and piezos in accordance  
16 with another embodiment of the invention.

#### 17 DETAILED DESCRIPTION OF THE PRESENT INVENTION

18 Referring to Fig. 2, a blister pack in accordance with the present invention  
19 comprises a bottom element 10 in the form of an elongate plastic tape or other flexible  
20 material, e.g. cloth, foil, paper, etc., having an overlying top element 12, carrying a  
21 plurality of spaced top crowned areas 14 containing controlled aliquots or doses of a

1 dry powder medication or drug or a liquid medication or drug. As illustrated in Fig. 2,  
2 the top crowned areas 14 are shaped as inverted cones and are mounted to bottom  
3 element 10 in regular spaced intervals. Areas 14 are substantially completely filled with  
4 a controlled aliquot or dose of a powder or liquid medication or drug. Typically, the  
5 blister pack of the present invention is provided as coil or a circular cartridge or unit  
6 dose pack. In use, the blister pack is uncoiled and advanced to a puncture stage where  
7 one or a plurality of controlled size holes 16 are punched through the top wall of the top  
8 crowned area 14.

9 The top crown areas 14 and bottom element 10 form an enclosed volume. The  
10 shape, height and volume of the blister pack, together with the size and number of  
11 holes punched through the top crowned area 14, play an important role in the de-  
12 aggregation and aerosolization of the powder or liquid material in the blister pack.

13 The three main phenomenon, besides others, which help in the de-aggregation  
14 and aerosolization of the material in the blister, are the Helm-Holtz resonator, the  
15 standing waves set-up in the blister pack and the vibrator frequency of the piezo. The  
16 Helm-Holtz resonator is formed by the holes punches in the top crown and the volume  
17 of the blister pack. The Helm-Holtz resonator helps to de-aggregate and eject the  
18 material from the blister pack. The frequency of the resonator will have to be optimized  
19 for maximum material de-aggregation and ejection efficiency.

20 The standing waves in the blister pack are determined by the height and shape of  
21 the blister. The standing waves help to lift and aerosolize the material in the blister.

1 The standing wave frequency is determined by the height and shape of the blister pack  
2 and will have to be optimized for maximum de-aggregation of the material in the  
3 blister.

4 The third main phenomenon is the piezo vibrator frequency. The piezo  
5 frequency should be such as to excite the Helm-Holtz resonator and establish the  
6 standing waves in the blister pack. The interface of the element 10 with the piezo  
7 vibrator should be such as to provide maximum coupling of the piezo vibrator energy  
8 into the blister pack.

9 It will be appreciated by those skilled in the art that these three phenomenon  
10 need to be optimized individually or in combination to achieve maximum de-  
11 aggregation and aerosolization of the powder or liquid material in the blister pack to  
12 make it suitable for delivery of medication or other compounds to the lungs.

13 The tape is advanced so that that area 18 of the bottom portion underlying the  
14 punctured top crowned area 14 is in contact with or adjacent the piezoelectric element  
15 20. The piezoelectric element 20 is then energized and couples with area 18, causing the  
16 blister pack to vibrate whereby to deaggregate and drive the powdered or liquid  
17 medication or drug out of the blister pack through holes 16.

18 Other shapes of blister packs made in accordance with the invention are shown  
19 in Figs. 3-5, and may include domed blister packs as illustrated in Fig. 3, dome/cone  
20 combinations as shown in Fig. 4, and cone/pill box combinations as shown in Fig. 5. In

1 all cases the lower element should be flat or nearly flat or at least have a generally  
2 flattened or slightly rounded surface for interfacing or coupling with the piezo.

3 A particular feature and advantage of the present invention is that the blister  
4 pack, when coupled to the piezo essentially acts as a miniature pump which expels the  
5 powder or liquid into the air stream.

6 The present invention offers several other advantages over the prior art. For one,  
7 the blister pack keeps the powdered or liquid medications or drugs freshly sealed and  
8 dry until just prior to use. Also, the blister pack keeps the powdered or liquid  
9 medications or drugs from flowing out or being lost, and allows the inhaler to be used  
10 in any orientation. Additionally, the size and shape of the top and bottom blister pack  
11 elements can be tuned to specific drug/piezo combinations for optimizing medication  
12 or drug delivery. Also, dosage size can be adjusted simply by changing the number of  
13 blister packs opened in the air channel. In such case, the multiple blisters may be  
14 opened simultaneously and driven by a common or by multiple piezos 20a, 20b . . . (see  
15 Figs. 6A and 6B), or sequentially. Also, if desired, two or more piezos may be  
16 employed, e.g. adjacent the bottom and sides of the blisters, and activated  
17 simultaneously or sequentially. Another advantage as noted supra is that the holes in  
18 the blister pack serve as a filter or sieve so as to prevent expulsion from the blister pack  
19 of aggregated or oversize particles. Thus, overdosing and/or waste is eliminated.

20 Various changes may be made in the foregoing without departing from the spirit  
21 and scope of the invention. For example, the blister pack of the present invention

